

## **REMARKS**

Reconsideration and withdrawal of the rejections of the claims are requested in view of the following remarks, which place the claims in condition for allowance.

### **I. STATUS OF CLAIMS AND FORMAL MATTERS**

Claims 1-14, 18-23, 26-49, 83, and 84 are under consideration in this application. Claims 1, 10, 11, 13, 29, 30, 32, 33, 35-37, 40-42, 45, 48, 49, 83, and 84 are amended and claims 2-6, 7-9, 14, 18-23, 26-28, 34, 46, and 47 are cancelled without prejudice, without admission, without surrender of subject matter, and without any intention of creating any estoppel as to equivalents.

Support for the amendment to the claims can be found throughout the specification as originally filed. For instance, support for the amendments to claims 1 and 83 can be found, as an example, on page 8, lines 11-30, on page 6, line 29 – page 7, line 17, on page 13, lines 20-21, and in Examples 4, 5, 10, 11, and 14.

The amendment to claims 1 and 83 directs the subject matter of the invention to a method of detecting modulators of Notch signal transduction involving activating T-cells and monitoring levels of one or more cytokines. Claims 10, 11, 13, 29, 30, 48, 49, and 84 are amended to correct for antecedent basis in light of the amendment to claims 1 and 83, and claims 32 and 33 are amended to clarify the units of the molecular weight of the candidate modulator. Claims 35-37 and 40-42 are amended to avoid depending from a cancelled claim, and claims 42 and 45 are amended to correct for typographical errors.

No new matter is added.

It is submitted that the claims herewith are patentably distinct over the prior art, and these claims are in full compliance with the requirements of 35 U.S.C. § 112. The amendments to the claims presented herein are not made for purposes of patentability within the meaning of 35 U.S.C. §§ 101, 102, 103 or 112. Rather, these amendments and additions are made simply to clarify the scope of protection to which Applicants are entitled. Furthermore, it is explicitly stated that these amendments should not give rise to any estoppel.

### **Objection to the specification**

The specification was objected to for containing an embedded hyperlink and for allegedly not providing an adequate description of Figures 4-30 in the Brief Description of the Drawings.

Applicants note that the specification has been amended to remove the hyperlink and to add to the description of Figures 4-30. Support for the amended description of the Figures can be found throughout the specification and figures, as outlined in the table below:

<u>Amended Figure Descriptions</u>	<u>Support in the Specification</u>
Description of Figure 4	Examples 2 and 3, and Figure 4
Description of Figure 5	Examples 2 and 6-8, and Figure 5
Description of Figure 6	Example 8 and Figure 6
Description of Figure 7	Example 3
Description of Figure 8	Example 4
Description of Figure 9	Example 5
Description of Figure 10	Example 6
Description of Figure 11	Example 7
Description of Figures 12A-12D	Example 8
Description of Figure 13	Example 10
Description of Figures 14A and 14B	Example 11 and Figures 14A and 14B
Description of Figures 15A and 15B	Example 11 and Figures 15A and 15B
Description of Figure 16	Example 11 and Figure 16
Description of Figure 17	Example 11 and Figure 17
Description of Figure 18	Example 11 and Figure 18
Description of Figure 19	Example 12
Description of Figures 20A and 20B	Example 13 and Figures 20A and 20B
Description of Figure 21	Example 14
Description of Figures 22A and 22B	Example 15
Description of Figure 23	Example 15 and Figure 23
Description of Figures 24A and 24B	Example 15
Description of Figures 25A and 25B	Example 15 and Figures 25A and 25B
Description of Figures 26A-26C	Example 15 and Figures 26A-26C
Description of Figure 27	Example 16
Description of Figure 28	Example 16

Description of Figure 29	Example 17
Description of Figure 30	Example 18

Accordingly, reconsideration and withdrawal of the objection to the specification are requested.

**Objection to the claims**

Claims 37 and 42 objected to for missing punctuation, while claim 45 was objected to for reciting two conjunctions consecutively. Further, claims 19, 37, and 38 recite acronyms that were not properly defined.

In response, claims 37, 42, and 45 are amended to correct for the typographical errors, and claim 37 was amended to define the acronym “TCR” as “T-cell receptor.” Claim 19 is cancelled, thereby rendering the objection to this claim moot. Accordingly, reconsideration and withdrawal of the objection to the claims are requested.

**II. THE REJECTIONS UNDER 35 U.S.C. § 112 ARE OVERCOME**

**Indefiniteness**

Claims 32, 33, 83, and 84 were rejected under the second paragraph of Section 112 as allegedly being indefinite for failing to distinctly claim the invention. The Examiner contends that these claims do not recite the units of the molecular weight of the candidate modulator, and that claim 83 does not indicate how the molecular weight is measured.

In response, claims 32, 33, 83, and 84 are amended to indicate that the units of molecular weight are Daltons, and to clarify that molecular weight is determined by SDS-PAGE. Clearly, the amended claims fully clarify and define the invention disclosed in the rejected claims

**Written Description**

Claims 1-14, 18-23, 26-49, 83, and 84 were rejected under the first paragraph of Section 112 as allegedly failing to comply with the written description requirement. The Examiner alleges that the claims are drawn to a broad genus of Notch signaling components/pathways, immune signaling components/pathways, second signals, and third signals without requiring any particular biological activity, conserved structure, or any other distinguishing features. The rejection is traversed.

In response, Applicants draw attention to the amended claims, wherein the subject matter of the invention is clarified and herein relates to a method for detecting modulators of Notch

signal transduction comprising activating T-cells, activating Notch signaling in the T-cells, contacting the T-cells with a candidate modulator, monitoring levels of one or more cytokines produced by the T-cells, and detecting a change in the level of the one or more cytokines due to the candidate modulator. Hence, the assertions regarding the allegedly broad genus of immune signaling pathways, second signals, and third signals encompassed by the claims are obviated in view of the claim amendments.

Furthermore, Applicants argue that the genus of Notch signaling components/pathways is indeed supported by the specification. Notably, the specification describes the Notch signaling pathway (see page 16, line 25 - 19, line 22), and notably discusses the scope of the pathway (page 16, lines 26-29), Notch receptors and how they are activated (page 17, lines 13-31), transduction from the Notch receptor (page 19, lines 9-18) and intracellular domain of Notch (page 18, line 13 – page 19, line 7).

Applicants assert that the specification also discloses various means of activating the Notch signaling pathway. For example, the specification describes and demonstrates the activation of the pathway via the binding of ligands to the Notch receptor (page 17, lines 25-31; page 26, line 25 – page 27, line 4; Examples 10-12), as well as activation of the pathway without the involvement of ligands (Example 18).

Therefore, there is sufficient written description in the specification to support the invention as disclosed in the instant claims.

### **Enablement**

Claims 1-14, 18-23, 26-49, 83, and 84 were rejected under the first paragraph of Section 112 as allegedly lacking enablement. The rejection is traversed.

The Examiner alleges that there would be a large quantity of experimentation necessary to practice the claimed invention, namely to activate all possible components or pathways of Notch signaling, to activate all possible components or pathways of immune signaling, and to identify and monitor a specific component/element of Notch or immune signaling.

In response, Applicants argue that the present invention is indeed enabled and that one of ordinary skill in the art can perform the method of the present invention without undue experimentation. Firstly, Applicants note that the scope of the claims is modified in view of the instant claims, wherein the present invention is herein directed to a method for detecting

modulators of Notch signal transduction comprising activating T-cells, activating Notch signaling in the T-cells, contacting the T-cells with a candidate modulator, monitoring levels of one or more cytokines produced by the T-cells, and detecting a change in the level of the one or more cytokines due to the candidate modulator. With this amendment in consideration, the breadth of the claims cannot be construed as broad in scope.

Applicants also assert that the specification provides ample guidance and working examples to enable the invention as claimed. For example, as described above, the specification describes the Notch signaling pathway, (page 16, line 25 - 19, line 22), how the pathway can be activated (page 17, lines 25-31), T-cells (page 56, line 18 – page 57, line 19), cytokines (page 56, line2 – page 57, line 2), and various assays that can be used to determine cytokine levels (page 72, line 30 – page 88, line 25). In addition, Examples 4 and 10-12 demonstrate the process of activating Notch signaling in T-cells, contacting the T-cells with a modulator, monitoring levels of cytokines produced by the T-cells, and then detecting a change in the level of cytokines due to the modulator.

Importantly, the subject matter considered as enabled by the specification was provided in the Office Action in the paragraph bridging pages 7 and 8, and instant claim 1 largely recites the same language. However, in contrast to the Office Action, Applicants argue that the scope of enablement is not limited to activation of T-cells with the ligand Delta only and to monitoring the levels of cytokines IL-10, IL-13, and IFN gamma only. It is well known in the art that there are many ways to activate Notch, and the specification discloses means that involve ligands such as Jagged/Serrate (see paragraph bridging pages 26 and 27) as well as means that do not involve ligands (see Example 18). Moreover, the detection of levels of IL-5 is amply disclosed in the specification, notably on page 13 lines 20-21, and in Example 11. Hence, the claimed subject matter relating to activation of T-cells and detection of cytokines is indeed enabled by the specification.

Therefore, one skilled in the art would not be subjected to undue experimentation to practice the claimed invention in light of (i) the modified scope of the claims, which is herein directed to monitoring cytokine levels as a measure of T-cell activation, (ii) the guidance in the specification, which sufficiently describes Notch signalling, Notch activation, and assays for measuring Notch signalling, especially relating to cytokine production, and (iii) the working

examples, which demonstrates the steps disclosed in the instant claims. Accordingly, reconsideration and withdrawal of all of the rejections under Section 112 is requested.

### **III. THE REJECTION UNDER 35 U.S.C. § 102 IS OVERCOME**

Claims 1, 2, 4, 5, 7-9, 12, and 31 were rejected under Section 102(b) as allegedly being anticipated by Gehring, *et al.* (WO 2001/03743; hereinafter “Gehring”). According to the Office Action, Gehring relates to a method of screening for agonists and antagonists of Notch pathway function comprising contacting the cell with the agonist/antagonist and concurrently treating the cell with a test agonist/antagonist, and then observing the fate of the cell. The rejection is traversed.

Again, Applicants draw attention to the claim amendments, wherein the claimed invention is directed to a method for detecting modulators of Notch signal transduction comprising activating T-cells, activating Notch signaling in the T-cells, contacting the T-cells with a candidate modulator, monitoring levels of one or more cytokines produced by the T-cells, and detecting a change in the level of the one or more cytokines due to the candidate modulator. Notably, Gehring does not teach or suggest activating Notch signaling in **T-cells**, or monitoring **cytokine levels** produced by the activated T-cells. Since the prior art reference must contain all of the elements of the claimed invention in order for the Section 102 rejection to stand, Applicants assert that the present invention is not anticipated by Gehring.

Accordingly, reconsideration and withdrawal of the Section 102 rejection are requested.

**CONCLUSION**

The application is in condition for allowance. Favorable reconsideration and allowance of the claims are requested. The Examiner is invited to contact the undersigned if any outstanding issues may be resolved by telephone.

Respectfully submitted,

FROMMER LAWRENCE & HAUG LLP  
Attorneys for Applicants

By: Anne-Marie C. Yvon  
Thomas J. Kowalski  
Reg. No. 32,147  
Anne-Marie C. Yvon, Ph.D.  
Reg. No. 52,390  
Tel (212) 588-0800